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The impact of albuminuria and cardiovascular risk factors on renal function

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Appendix 1

How to measure the prevalence of microalbuminuria in relation to age and gender?

Jacobien C. Verhave, Hans L. Hillege, Dick de Zeeuw, Paul E. de Jong

Am J Kidney Dis 2002;40:436-437, Letter to the editor

Letter to the editor to react on the article:**Microalbuminuria in the US population: Third National Health and Nutrition Examination Survey**

By

C. A. Jones, M.E. Francis, M.S. Eberhardt, B. Chavers, J. Coresh, M. Engelgau, J.W. Kusek, D. Byrd-Holt, V. Narayan, W.H. Herman, C.P. Jones, M. Salive, L.Y. Agodoa

Am J Kidney Dis 2002;39:445-459

In diabetic subjects microalbuminuria indicates an increased risk for renal disease progression and cardiovascular morbidity and mortality. In non-diabetic populations research findings suggest that microalbuminuria may be an important risk marker. In 22,244 participants of the NHANES III study, US estimates of the prevalence of microalbuminuria, defined as a albumin-creatinine ratio 30-299 mg/g, were described. Of the diabetic subjects 28.8% had microalbuminuria, of the hypertensive subjects 16.0% were found microalbuminuric and of the non-diabetic nonhypertensive subjects 5.1%. The prevalence of microalbuminuria was significantly lower in males (6.1%) compared to females (9.7%). In subjects > 40 years of age, albuminuria (ACR \geq 30 mg/g) was independently associated with older age, non-Hispanic black and Mexican American ethnicity, diabetes, hypertension, and elevated serum creatinine concentration.

How to measure the prevalence of microalbuminuria in relation to age and gender?

Dear Sir,

Recently, two NHANES III database publications discussed the difference of the prevalence of microalbuminuria in males and females. Jones *et al* concluded that microalbuminuria, defined as a urinary albumin-creatinine ratio (ACR) of 30-299 mg/g, was found more frequently in females (9.7%) than in males (6.1%) (1). However, the higher prevalence was only observed in the age groups of younger females (6-19 and 20-39 years), but not in the older ages. They also show that the difference between both genders is notably reduced when defining microalbuminuria as a urinary albumin concentration (UAC) of more than 30 mg/L: 11.8 \pm 0.6 in females versus 10.9 \pm 0.5 in males. The discrepancy in the finding of a gender difference when using ACR versus UAC can only be explained by the well-known fact that urinary creatinine excretion in women is lower than in men. Interestingly, at the same time another publication from the same database, but from other authors, showed that the use of one ACR value for both sexes was inaccurate (or incorrect) (2). These authors argued that a sex-specific ACR has to be used: for males 17-249 mg/g and for females 25-354 mg/g. Although both observations are highly interesting and important, the conclusions are drawn from spot sample urine collections which is not the gold standard to measure urinary albumin excretion. Spot urine sampling in fact has several disadvantages including the bias of varying urine concentrations of the samples, as well as variation induced by the diurnal rhythm of

both albumin excretion as well as creatinine excretion. Therefore, the use of 24 hour urine collections is recommended as the gold standard to measure urinary albumin excretion rate.

We recently studied and published on the prevalence of microalbuminuria in the general population of the city of Groningen (n= 40,856; aged 28-75; (3)). In a selected cohort (n= 8,592) from this population we sampled 24 hour urine for albumin and creatinine measurements (4). This allows us to analyze the total amount of albumin per day (UAE) as well as the albumin concentration in that sample (UAC) and the albumin concentration corrected for creatinine (ACR). The table shows the prevalence of microalbuminuria in males and in females as well as the prevalence in the oldest (70-75 years) versus the youngest age group (28-40 years) in both genders according to the different criteria.

The data show that microalbuminuria is more prevalent in men than in women and that the prevalence increases with age, which is more pronounced in men than in women. The results are almost identical for UAE and UAC. However, the results are quite different when the ACR criterion was used. The single cut off ACR underestimates the prevalence of microalbuminuria in men while it overestimates the prevalence with increasing age for both genders. Although the sex-specific ACR gives a more accurate estimate of the prevalence of microalbuminuria in both genders, it strongly overestimates the increase over age in women. The discrepancy in results can be attributed to the values of urinary creatinine (Ucreat): Ucreat is not only much lower in women than in men but there is also a more progressive decline in Ucreat with increasing age in women when compared to men.

We conclude that in large population studies UAC is a reliable measurement to estimate the prevalence of microalbuminuria in both sexes and irrespective of age when compared with the gold standard UAE. Although creatinine correction (ACR) is very often applied to control for variations in urinary flow rate, this technique should not be used to study sex and age-related differences in the prevalence of MA. Creatinine excretion is not only lower in women than in men, but also diminishes with age and, therefore, ACR needs both sex and age specific discriminator values.

Table 1. Prevalence of microalbuminuria according to different criteria.

Criterion for microalbuminuria	Prevalence of Microalbuminuria (%)				
	Male	Female	Male/ Female	Old/young	
				Male	Female
UAE 30-300 mg/d	16.7	9.1	1.8	6.2	2.6
UAC 20-200 mg/L	17.5	10.1	1.8	6.3	2.4
ACR 30-300 mg/g	10.5	8.1	1.3	8.3	3.4
ACR male 17-249/ female 25-354 mg/g	19.2	10.1	1.9	6.7	3.7
	Male	Female	Male/ Female	Old/young	
				Male	Female
Mean Ucreat (mg/L)	113.4	75.6	1.4	0.8	0.7
Mean Uvolume (mL/d)	1595	1695	1.0	1.1	1.0

References

1. Jones CA, Francis ME, Eberhardt MS, Chavers B, Corsh J, Engelgau M, Kusek JW, Byrd-Holt D, Narayan V, Herman WH, Jones CP, Salive M, Agodoa LY. Microalbuminuria in the US population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis.* 2002;39:445-459.
2. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J. Am. Soc. Nephrol.* 2002;13:1034-1039.
3. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns JGM, van Gilst WH, de Zeeuw D, de Jong PE. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J. Intern. Med.* 2001;249:519-526.
4. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann. Intern. Med.* 2000;133:585-591.

Appendix 2

Obesity and target organ damage: the kidney

Paul E. de Jong, Jacobien C. Verhave, Sara-Joan Pinto-Sietsma, Hans L. Hillege

Int J Obes Relat Metab Disord. 2002;26 Suppl 4:S21-24, Review

Abstract

Obesity is a risk marker for progressive renal function loss in patients with known renal disease. There is however increasing evidence that obesity may also damage the kidney in otherwise healthy subjects. There appears to be an intriguing parallel between the renal effects of obesity and those of diabetes. First, an increased renal blood flow and glomerular filtration rate has been described in obesity and second, microalbuminuria is found to be related to obesity. These two events are known to predict future loss of renal function in diabetes. The mechanism responsible for the renal damage in obesity has not been established but there is evidence suggesting that this might be related to both hormonal changes as well as low-grade inflammation.

Keywords

Obesity, glomerulosclerosis, microalbuminuria, glomerular filtration rate.

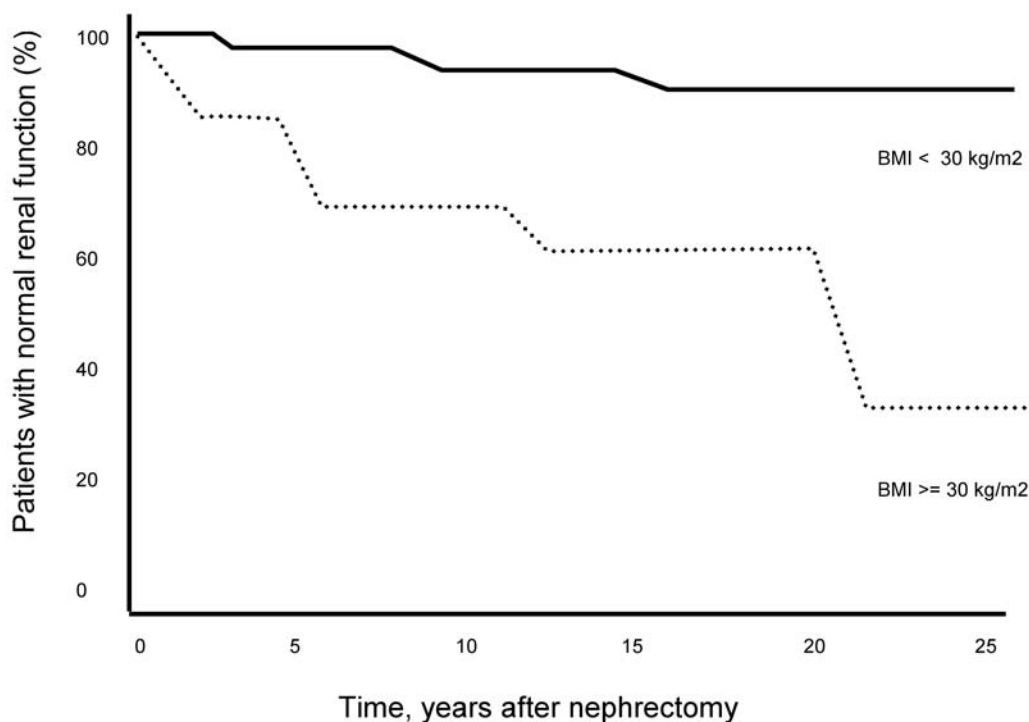
Introduction

The prevalence of obesity is increasing world-wide and the impact obesity has on metabolic and cardiovascular diseases has been well documented. So far, less attention has been paid to the impact of obesity on the kidney. In this overview we will discuss 1) the evidence that obesity may enhance the progression of renal function deterioration to end-stage renal failure in subjects with known pre-existing renal disease, 2) the renal effects of obesity in otherwise healthy subjects, and 3) the potential mechanisms of obesity-induced renal damage.

The impact of obesity on renal function loss in pre-existing renal disease

Praga *et al* (1) showed in a follow-up study of 73 patients the long-term effects of obesity on the kidney. These patients had undergone unilateral nephrectomy. Fourteen of the 73 patients were obese at the time of nephrectomy. At 20-year follow up, most of the non-obese subjects but only 30%-40% of the obese subjects still had normal renal function (figure 1).

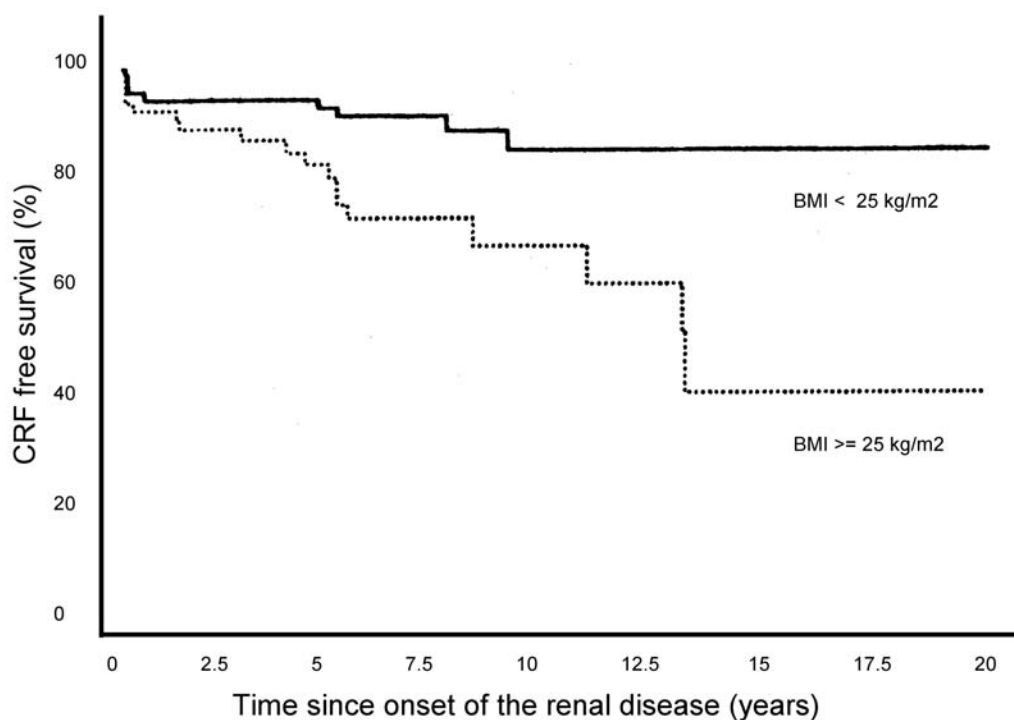
Figure 1. The percentage of patients remaining with normal renal function after unilateral nephrectomy in those with obesity or not at the time of nephrectomy (with permission of the authors, from ref 1).



Furthermore, Bonnet *et al* (2) showed in another recent study in 162 patients with IgA nephropathy a similar phenomenon. The presence of an elevated body mass index (≥ 25 kg/m²) at the time of renal biopsy correlated with the severity of the pathological abnormalities and with the clinical progression to end-stage renal failure (figure 2). The type of renal abnormalities seen in obese patients has been investigated by Kasiske *et al* (3). They compared the clinical and histological pattern in 17 patients with massive obesity (mean weight 126 kg) and marked proteinuria with an age- and sex-matched control group of 34 patients with similar clinical presentation but normal body weight (mean weight 68 kg). Although urinary protein excretion was similar in the two groups, serum albumin was higher in the obese subjects, probably because proteinuria develops more gradually in people with obesity and the liver is still able to compensate for the increased protein loss. With respect to the histological data, most of the obese patients had a focal glomerulosclerosis while most of the subjects in the control group had minimal change nephrotic syndrome or membranous nephropathy.

It has recently been reported that the incidence of obesity related glomerulopathy, defined by the authors of a biopsy based study as focal segmental glomerulosclerosis and glomerulomegaly, increased ten-fold over the last 15 years (4). Therefore, if obesity in some specified patient groups results in glomerulosclerosis, what is the impact of obesity for the kidney in the general population?

Figure 2. The percentage of subjects remaining free of chronic renal failure (CRF) after the diagnosis of IgA nephropathy according to the presence of an elevated body mass index (with permission of the authors, from ref 2).



Impact of obesity on the kidney in the general population

To gain more insight, we first consider the mechanism for diabetic nephropathy, since there are now data indicating that diabetes and obesity may have similar effects on the kidney. In the initial stages of type I diabetes, glomerular filtration rate tends to increase due to increased glomerular capillary pressure, a process called glomerular hyperfiltration (5). This may be followed by an increased urinary albumin excretion. This albumin loss may then reach the range of microalbuminuria, that is 30-300 mg/24h. This phase of microalbuminuria is followed by a progressive fall in glomerular filtration rate, in parallel with a further rise in urinary albumin excretion, leading to the development of overt proteinuria and, eventually, end-stage renal failure (5).

Microalbuminuria is not only the predominant predictor of progressive renal failure, but also of progressive cardiovascular disease in diabetes. Within this perspective, it has been speculated that microalbuminuria represents the renal expression of a generalized disorder characterized by an increased endothelial permeability. That endothelial damage may underlie the link between an increased urinary albumin excretion and the increased risk of cardiovascular disease. The question that has been addressed in recent research is whether these predictors (that is glomerular hyperfiltration and microalbuminuria) apply only to patients with diabetes or are also relevant to the general population.

It has been shown previously that an increased body mass index is associated with microalbuminuria, especially in hypertensive subjects (6). We studied the impact of obesity on renal function in the general population in a sub-analysis of the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, that was initiated to study the impact of microalbuminuria for renal and cardiovascular risk in the general population (7,8). To that purpose we determined the prevalence of microalbuminuria in the general population, aged 28-75 years (7). We found microalbuminuria (urinary albumin concentration > 20 mg/L) to be present in 16.4% of subjects known with diabetes, in 11.5% of those known with hypertension and in 6.6% of "healthy" subjects who were not known to have either diabetes or hypertension (7). Presented differently, 75% of all cases of microalbuminuria occurred in non-diabetic, non-hypertensive individuals.

If so many subjects have microalbuminuria, what then is the cause of microalbuminuria in these non-diabetic and non-hypertensive subjects? In this sub-analysis of the PREVEND study, we questioned to what extent microalbuminuria is mediated by obesity. To that purpose, we used the data of the 8,592 subjects in which more detailed physical and laboratory examinations were done, including two 24 hour urine collections to measure 24 hour urinary albumin excretion. Microalbuminuria was defined according to the classical criteria of 30-300 mg per 24 hours (8). Data from 542 subjects were excluded from this analysis because urinary albumin excretion was not reliable due to the presence of erythrocyturia and/or leukocyturia and/or missing data. In table 1 we give the data on the 8,592 subjects according to body mass index and separated by gender. The table shows the number of subjects with a normal body mass index (< 25 kg/m²), overweight (25-30 kg/m²) and obesity (> 30 kg/m²). In men about 47% was overweight and another 14% was obese. In women 34% was overweight and another 16% was obese. In both genders a higher body mass index was associated with higher levels of cardiovascular risk factors, such as a higher age, blood pressure, glucose and cholesterol level. Furthermore, it was also associated with a higher C-reactive protein level and a greater 24h urinary albumin excretion. In men the

Table 1. Population characteristics of PREVEND study cohort, separated for body mass index and gender.

		Male			Female		
BMI	kg/m ²	< 25	25-30	> 30	< 25	25-30	> 30
No.		1597	1969	597	1946	1302	639
Age	yrs	46.4 ± 12.6	52.4 ± 12.8	53.2 ± 11.5	43.8 ± 10.7	51.0 ± 12.3	53.4 ± 12.1
Systolic BP	mmHg	126.3 ± 15.8	136.8 ± 18.4	142.8 ± 18.3	116.9 ± 17.5	129.1 ± 21.0	135.9 ± 21.1
Diastolic BP	mmHg	73.3 ± 8.7	78.5 ± 9.3	81.2 ± 9.3	68.5 ± 8.6	73.0 ± 8.9	74.3 ± 8.9
P glucose	mmol/L	4.7 ± 1.0	5.1 ± 1.3	5.5 ± 1.6	4.4 ± 0.6	4.9 ± 1.2	5.3 ± 1.6
P cholesterol	mmol/L	5.4 ± 1.1	5.8 ± 1.1	6.0 ± 1.0	5.3 ± 1.1	5.9 ± 1.2	5.9 ± 1.1
CRP*	mg/L	0.7 (0.3-1.8)	1.4 (0.7-2.8)	2.2 (1.2-4.2)	0.8 (0.3-1.9)	1.7 (0.8-3.5)	3.4 (1.6- 6.5)
UAE*	mg/24h	8.5 (6.3-14.5)	11.3 (7.2-24.0)	17.5 (9.7-40.5)	7.7 (5.6-12.2)	8.0 (5.8-14.1)	10.1 (6.6- 20.4)

BMI = body mass index; BP = blood pressure; P = plasma; CRP = C-reactive protein; UAE = urinary albumin excretion

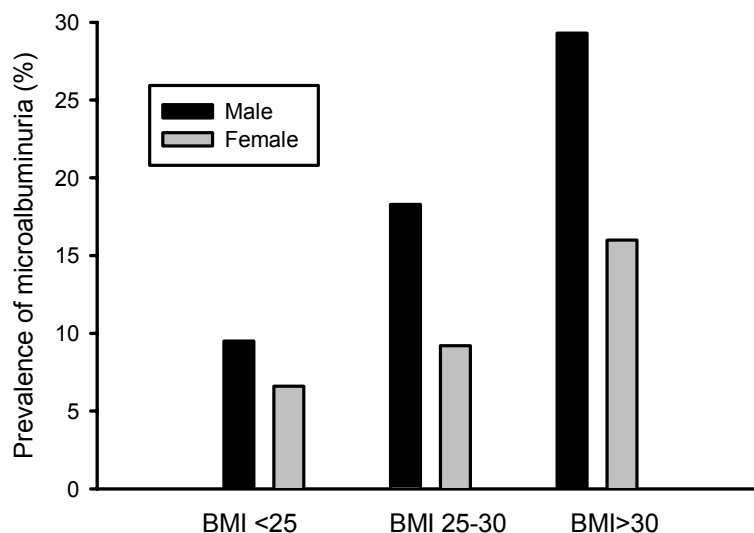
* median and 25-75% interval

prevalence of microalbuminuria increased from 9.5% in those with a normal body weight to 18.3% in those with overweight and to 29.3% in those with frank obesity. In women these percentages were 6.6, 9.2 and 16.0%, respectively (figure 3). In a multivariate analysis we showed that body mass index was independently associated with urinary albumin excretion and that there was an interaction between gender and body mass index, men having a more steeper rise in urinary albumin excretion at increasing body mass index in comparison with women (9).

In diabetes, as mentioned before, glomerular hyperfiltration is present at the time that microalbuminuria develops (5). Thereafter glomerular filtration rate starts to decrease and urinary albumin excretion rises further to macroproteinuric ranges. We previously showed that the same phenomenon might be present in non-diabetic subjects (10). Creatinine clearance was higher in subjects with a high normal albumin excretion (15-30 mg/day) than in controls (albumin excretion 0-15 mg/day) and was still elevated in microalbuminuric (albumin excretion 30-300 mg/day) persons while it was lower in the macroproteinuric (albumin loss > 300 mg/day) subjects. After adjustment for age, gender, body mass index, glucose, family history for diabetes, blood pressure and smoking, high-normal albuminuria and microalbuminuria were independently associated with an elevated filtration (RR 1.8 [95%CI: 1.30-2.51] and 1.7 [1.17-2.45]). Macroproteinuria was independently associated with a diminished filtration (4.3[1.97-9.36]) (10). This pattern is similar to that described in diabetics, with initial glomerular hyperfiltration, followed by gradual loss of renal function. This suggests that the higher risk for microalbuminuria is associated with a higher risk for glomerular hyperfiltration and ultimately impaired glomerular filtration in non-diabetic subjects. These data are compatible with results of accurate renal function studies, in which it was shown that obese subjects indeed have an elevated renal blood flow and glomerular filtration rate (6,11).

The hypothesis that glomerular hyperfiltration and microalbuminuria underlie the pathogenesis of glomerular sclerosis in obesity, is substantiated by recent experiments in hyperphagic obese Zucker rats. That study showed that glomerular injury correlated with hyperphagia induced glomerular hyperfiltration.

Figure 3. The percentage of men and women having microalbuminuria according to body mass index.



It moreover, showed that food restriction directly prevented the glomerular hyperfiltration and ultimately prevented the development of glomerular sclerosis. Interestingly, the authors also showed that the earlier the food restriction was instituted, the better the glomerulosclerosis could be prevented (12).

Mechanism of obesity-induced renal damage

What then is the mechanism behind the obesity related renal damage? Hormonal factors may be involved. First, insulin resistance, generally present in obesity, could be one of the mechanisms, as insulin resistance induces systemic (13) and intraglomerular (14) hypertension as well as mesangial hypertrophy and increased mesangial matrix production (15). The potential role of leptin is also interesting. It is a small peptide hormone that is mainly, but not exclusively, produced in adipose tissue. Leptin serum concentration is related to body fat (16). Leptin, amongst others, has direct effects on renal pathophysiology. In glomerular endothelial cells, leptin stimulates cellular proliferation, transforming growth factor- β 1 synthesis, and type IV collagen production. Conversely, leptin upregulates synthesis of the TGF- β type II receptor in mesangial cells, but not of TGF- β 1, and stimulates glucose transport and type I collagen production (17). These data suggest that leptin triggers a paracrine interaction in which glomerular endothelial cells secrete TGF- β , to which sensitized mesangial cells may respond. Both cell types increase their expression of extracellular matrix in response to leptin (18). Interestingly to note, infusion of leptin in normal rats for 3 weeks resulted in glomerulosclerosis and proteinuria (17).

Finally, the role of an inflammatory process triggered by obesity should be mentioned as a mechanism for the obesity related renal changes. It is known that adipocytes produce cytokines and that C-reactive protein (CRP) levels are elevated in obesity, suggesting a state of low-grade systemic inflammation (19,20). Table 1 shows CRP level to increase with body mass index, although this increase appears to be more prominent in females than in males, while the body mass index-associated rise in urinary albumin excretion seems to be more prominent in males than in females. This rise in CRP levels is considered to reflect the low-grade inflammatory condition associated with atherosclerosis (21). Indeed an elevated CRP is found to predict future cardiovascular disease. Several studies with long follow-up have shown that increased levels of this inflammatory marker are associated with increased risk of coronary heart disease, stroke and peripheral vascular disease (22). We similarly showed that higher quartiles of CRP levels are associated with a higher relative risk of impaired glomerular filtration, after adjustment for other factors associated with a raised CRP level (23).

Conclusion

Obesity may lead to glomerular hyperfiltration, increased urinary albumin loss and a progressive loss of renal function, associated with a focal segmental glomerulosclerosis. This may be present not only in subjects with previously manifest renal disease, but also in otherwise healthy subjects. These renal changes may well be related to insulin resistance and/or hyperleptinemia, but may also be mediated by as a state of low-grade inflammation induced by obesity. Microalbuminuria may be an easy to measure marker to detect risk of progressive renal failure in obesity.

